REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendment are respectfully requested.

The specification has been amended to conform the description of Figure 5 with the labeling of the formal drawings submitted herewith. The specification has been amended to remove the embedded hyperlink.

Claim 15 has been revised to define the invention with additional clarity. The claim as presented is fully supported by an enabling disclosure.

The Examiner is again requested to reconsider the requirement for restriction and rejoin the subject matter of Groups I-IV. As pointed out previously, DDRT 2 (SEQ ID NO:34 (Group I)), DDRT 7 (SEQ ID NO:50 (Group II)), DDRT 16 (SEQ ID NO:40 (Group III)) and DDRT 26 (SEQ ID NO:14 (Group IV)) are derived from the <u>same</u> <u>predicted</u> gene F35E8.11 (see page 31 of the application). Thus a thorough search of the elected Group would <u>necessarily</u> include the subject matter of non-elected Groups I, II and IV.

In maintaining the requirement for restriction, the Examiner articulates his understanding

that the sequences set forth in SEQ ID NOs:34, 50, 40 and 14 are alternatively spliced from predicted gene F35E8.11 and encode different proteins each having different chemical structure and different function.

The Examiner indicates that it is in light of this reasoning that he maintains

that Inventions I-IV are distinct and the sequences embraced by each are separately searched.

The Examiner goes on to indicate that absent evidence showing that SEQ ID NOs:34, 50, 40 and 14 do not encode different proteins, the restriction requirement over Groups I-IV is maintained.

The Examiner's understanding that SEQ ID NOs:34, 50, 40 and 14 are alternatively spliced from the predicted gene F35E8.11 and encode different proteins is in error. No basis is seen in the specification (or in the record) for such an understanding. Respectfully, the Examiner appears to have confused the reference in the application to differentially expressed mRNAs with alternative spliced forms of the F35E8.11 gene. Pages 24-31 of the specification, to which the Examiner refers, make reference to the former – not to the latter.

Table II of Example 2 shows that DDRT 2, 7, 16 and 26 are derived from the same gene (note the "•" after each and footnote "b". Table III of Example 4 shows that DDRT 2, 7, 16 and 26 are derived from the gene F35E8.11 (see also page 31, lines 10 and 11). Nothing is said that would have suggested that DDRT 2, DDRT 7, DDRT 16 and DDRT 26 are alternative spliced forms of that gene.

For the avoidance of any doubt, submitted herewith is a Multiple Sequence
Alignment" demonstrating that DDRT 2, DDRT 7, DDRT 16 and DDRT 26 are all EST's
from the same region of an mRNA. Clearly, they are <u>not</u> alternative spliced forms of the
gene (in fact, they all come from the last exon of the gene) (as will be seen from the

FREEDMAN et al Appl. No. 09/437,450 March 15, 2004

Legend, AF071362 corresponds to DDRT 2, AF071398 to DDRT 7, AF071356 to DDRT 16 and AF071379 to DDRT 26).

Given that it is now clear that the Examiner's reason for requiring restriction results from a clear misunderstanding, reconsideration and withdrawal of the requirement for restriction are requested.

On page 4 of the Action, the Examiner indicates that corrected drawings are required. Formal drawings are submitted herewith. The Examiner is requested to indicate in the next communication that the new drawings have been accepted.

The Examiner's objection to the specification, set forth on page 5 of the Action, is most in view of the above-noted revision.

The Examiner indicates that the specification must be amended to make reference to the provisional application from which this application claims priority. In this regard, the Examiner's attention is directed to the amendment set forth on the coversheet of November 10, 1999 that directs entry of the priority claim. Acknowledgement that compliance with the conditions for receiving benefit of the provisional application is requested.

Claims 7, 11 and 15 stand rejected under 35 USC 101 as allegedly lacking utility. The rejection is traversed.

The rejection of the claims as lacking utility appears based on certain misunderstandings. The following comments are intended to address those points of

confusion and, in so doing, make it clear that the invention is indeed supported by a specific and substantial asserted utility.

At the time of filing the subject application, the *C. elegans* genome had been essentially sequenced (relevant references and accession numbers are given on page 9). The data provided in the Examples, note particularly Example 2, make it clear that DDRT 16 (SEQ ID NO:40) is a cDNA fragment corresponding to a differentially expressed mRNA. Table II shows that DDRT 16, DDRT 2, DDRT 7 and DDRT 26 all derive from the *C. elegans* gene F35E811.

As indicated in Table II, greater than a 4-fold increase in DDRT 16 mRNA level was observed following cadmium exposure. The responsiveness of the gene from which DDRT 16 derives to a stressor such as cadmium makes it useful as a biomonitor.

The Examiner contends that at the time the claimed invention was made, the full length sequence of the CDR-1 gene was not available and that the DDRT 16 sequence can only be used for further research (e.g., obtaining the full length sequence). This comment overlooks explanation provided in the Supplemental Amendment filed August 6, 2001 which details how, based on the information provided in the subject application and information readily available at the time of filing, one could readily access the complete genomic sequence of the gene encoding DDRT 16 and the complete cDNA and protein sequences.

The disclosure of the instant application makes it clear that the presence of cadmium in an environment can be determined by assaying for elevated levels of

cadmium-responsive mRNA's or proteins (see, for example, pages 12 and 13). Cadmium is a serious occupational and environmental toxin, thus the identification of DDRT 16 has clear utility as its corresponding mRNA increases greater than 4-fold following cadmium exposure.

In view of the above, reconsideration is requested.

Claims 7, 11 and 15 stand rejected under 35 USC 112, first paragraph, as the disclosure allegedly fails to teach how to use the claimed invention. This rejection is based on the alleged lack of utility, discussed above. Thus, the foregoing comments offered in response to the rejection under 35 USC 101 are equally applicable here.

As indicated above, one utility of the claimed invention is in the context of a biomonitor. The Examples make clear that, on exposure to cadmium, mRNA levels are significantly increased. The disclosure at page 12 describes means for assaying levels of expression (see also Examples). Such approaches are standard in the art. At page 13 of the application, the use of transgenic organisms comprising cadmium-responsive sequences as biomonitors to measure the levels of bioavailable cadmium is described.

The application provides all that is necessary - the identification of the cadmium-responsive sequence and means for measuring the level of expression upon exposure to the stressor. Nothing more should be required to satisfy the requirement of 35 USC 112, first paragraph. Reconsideration is thus requested.

FREEDMAN et al Appl. No. 09/437,450 March 15, 2004

Claim 15 stands rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revision. Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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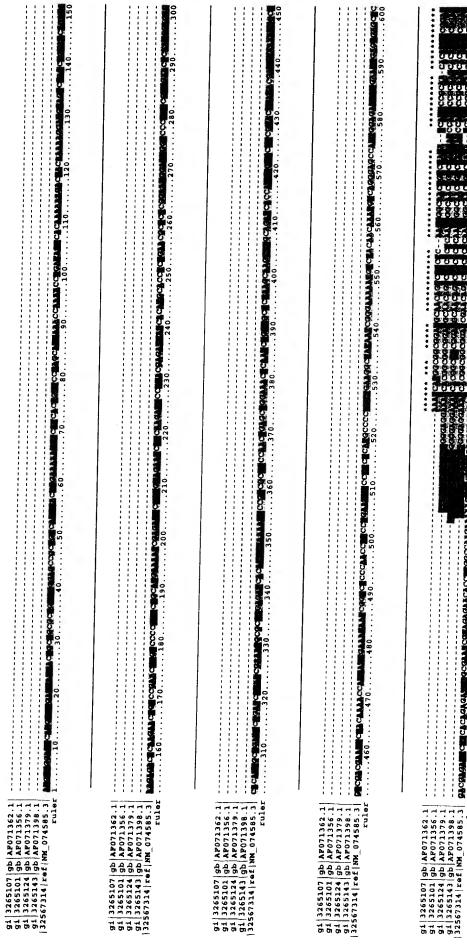
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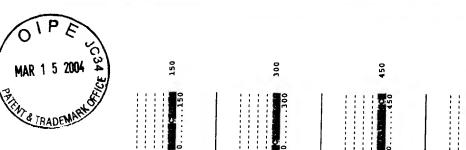
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Facsimile: (703) 816-4100

CLUSTAL X (1.81) MULTIPLE SEQUENCE ALIGNMENT

Page 1 of 2





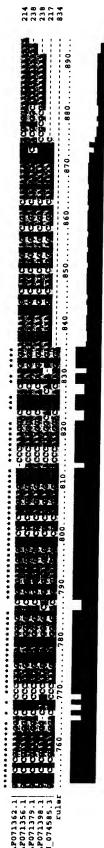
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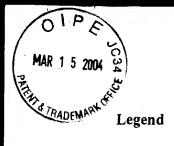


CLUSTAL X (1.81) MULTIPLE SEQUENCE ALIGNMENT

Page 2 of 2

AP071362 AP071356 AP071379 AP071396	
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101 124 143 4 F	
265 265 265 731	
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 $>gi|32567314|ref|NM_074585.3|$ Caenorhabditis elegans Cadmium Responsive CDR-1 (cdr-1), mRNA

>gi|3265107|gb|AF071362.1| AF071362 mRNA from cadmium-responsive gene Caenorhabditis elegans cDNA clone DDRT2, mRNA sequence

>gi|3265143|gb|AF071398.1| AF071398 mRNA from cadmium-responsive gene Caenorhabditis elegans cDNA clone DDRT7, mRNA sequence

>gi|3265101|gb|AF071356.1| AF071356 mRNA from cadmium-responsive gene Caenorhabditis elegans cDNA clone DDRT16, mRNA sequence

>gi|3265124|gb|AF071379.1| AF071379 mRNA from cadmium-responsive gene Caenorhabditis elegans cDNA clone DDRT26, mRNA sequence

Small gaps or single nucleotide differences are the result of the technology used to generate the EST's and do not represent alternative spliced forms of the gene.

The poly T heads in some of the EST's are produced during the differential display process, and are not derived from the gene.